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UTILITY

PATENT APPLICATION

TRANSMITTAL

Attorney Docket No. X-10675

First Named Inventor or Application Identifier

Michael Rosario DeFelippis, Michael Allen Dobbins,
Bruce Hill Frank, Shun Li and Dawn Marie Rebhun

Express Mail Label No.

EL041989505US

Application Elements

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee Transmittal Form (Submit an original, and a duplicate for fee processing)

6. ☐ Microfiche Computer Program (Appendix)

2. ☒ Specification [Total 29 Pages]
(preferred arrangement set forth below)

7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)

- Descriptive title of the invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claims

- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

Abstract of the Disclosure

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))

9. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney

10. ☐ English Translation Document (if applicable)

11. ☒ Information Disclosure Statement (IDS)/PTO-1449 ☒ Copies of IDS Citations

12. ☐ Preliminary Amendment

13. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)

14. ☐ Small Entity Statement(s) ☐ Statement filed in prior application, Status still proper and desired

15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)

16. ☐ Other: XXX

☐ Drawing(s) (35 USC 113) [Total Sheets ☐

☐ Oath or Declaration [Total Pages ☐

a. ☐ Newly executed (original or copy)

b. ☐ Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed) [Note Box 5 below]

1. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference (useable if Box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: _____

18. CORRESPONDENCE ADDRESS

Customer Number or Bar Code Label

(Insert Customer No. Or Attach bar code label here)

or

Correspondence address below

NAME Steven P. Caltrider

Eli Lilly and Company

ADDRESS Lilly Corporate Center

Patent Division DC: 1104

CITY Indianapolis

STATE Indiana

ZIP CODE 46285

COUNTRY U.S.A.

TELEPHONE 317-276-0757

FAX 317-276-5172

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FEE TRANSMITTAL

Note: Effective October 1, 1997.

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT (\$ 790.00)

METHOD OF PAYMENT (check one)

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:
- Deposit Account Number 05-0840
- Deposit Account Name Eli Lilly and Company
- ☒ Charge Any Additional Fee ☐ Charge the Issue Fee Set in 37 CFR 1.18 at the Required Under 37 CFR 1.16 and 1.17 Mailing of the Notice of Allowance
2. ☐ Payment Enclosed.
- ☐ Check ☐ Money Order ☐ Other

FEE CALCULATION

1. FILING FEE

Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	790
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) (\$ 790.00)

2. CLAIMS

Total Claims	Extra	Fee from below	Fee Paid
14	-20=	0	X 22 =
2	-3=	0	X 82 =
Multiple Dependent Claims			X =

Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim
109	82	209	41	Reissue independent claims over original patent
110	22	210	11	Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$)

3. ADDITIONAL FEES

Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid
105	130	205	65	Surcharge-late filing fee or oath	
127	50	227	25	Surcharge-late provisional filing fee or cover sheet. Non-English specification	
139	130	139	130		
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	950	217	475	Extension for reply within third month	
118	1,510	218	755	Extension for reply within fourth month	
128	2,060	228	1,030	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive-unavoidable	
141	1,320	241	660	Petition to revive-unintentional	
142	1,320	242	660	Utility issue fee (or reissue)	
143	450	243	225	Design Issue Fee	
144	670	244	335	Plant Issue Fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt.	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))	
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify)

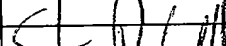
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SUBTOTAL (3) (\$)

SUBMITTED BY

Typed or Printed Name Steven P. Caltriden

Signature 

Complete (if applicable)

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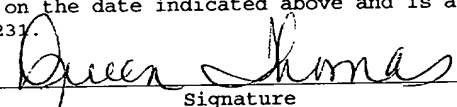
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Title**STABLE INSULIN FORMULATIONS****Cross-Reference**

5 This application claims the benefit of U.S.
Provisional Application No. 60/053,089, filed June 13, 1997.

Background of the Invention

10 The present invention is in the field of human
medicine, particularly in the treatment of diabetes and
hyperglycemia by the administration of monomeric insulin
analogs. More specifically, the present invention relates
to formulations of monomeric insulin analogs that have
superior long-term physical stability when exposed to high
15 mechanical energy input and high temperature.

 Stable formulations of therapeutic agents are
particularly required for use in delivery devices that
expose these agents to elevated temperatures and/or
mechanical stress. For example, stable insulin formulations
20 are required for use in continuous infusion systems and pen
delivery devices. Current formulations provide only limited
stability in these types of delivery devices.

 In continuous infusion systems, a fluid containing
a therapeutic agent is pumped from a reservoir, usually to a
25 subcutaneous, intravenous, or intraperitoneal depot. The
reservoir, which must be refilled periodically, is attached
to the patient's body, or is implanted in the patient's
body. In either case, the patient's body heat and body

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motion, plus turbulence in the tubing and pump impart a relatively high amount of thermo-mechanical energy to the formulation. In the interest of minimizing the frequency with which the reservoir is refilled, and of minimizing the size of the reservoir, formulations having a relatively high concentration of the therapeutic agent are highly advantageous.

Massey and Sheliga, U.S. Patent No. 4,839,341 (Eli Lilly and Company, 1989) discuss the challenges involved in providing stable insulin formulations for continuous infusion, and present a thorough review of the art through about 1984. The challenges are even greater at the present time because insulin formulations that are stable for 1 to 3 months are now demanded.

Injector pens have also been developed to aid diabetics in measuring and administering an accurate and controlled dose of insulin. Generally, these pens are secured onto a cartridge having a particular quantity of liquid medication sealed therein. The cartridge includes a plunger and a mechanism for advancing the plunger in the cartridge in such a manner to dispense the medication. Injector pens may be reusable or disposable. In reusable pens, a user can change a spent cartridge and reset the leadscrew of the pen back to its initial position. In a disposable pen, the cartridge is permanently captured in the pen which is disposed of after the contents of the cartridge have been exhausted. Formulations of insulin used in these pens are exposed to physical stress and limited stability is usually observed.

With the introduction of new monomeric insulin analogs for the treatment of diabetes, there is a need to utilize these compounds in treatment regimes that can compromise the inherent stability of the formulations. Rapid-acting insulins, known as monomeric insulin analogs, are well-known in the art, and are disclosed in Chance, et

al. U.S. patent No. 5,514,646, issued May 7, 1996; Brems, et al., *Protein Engineering*, 6:527-533 (1992); Brange, et al., EPO publication No. 214,826 (published March 18, 1987); and Brange, et al., *Current Opinion in Structural Biology* 1:934-940 (1991). Monomeric insulin analogs are absorbed much faster than is insulin, and are ideally suited for postprandial control of blood glucose levels in patients in need thereof. They are also especially well-suited for administration by continuous infusion for both prandial and basal control of blood glucose levels because of their rapid absorption from the site of administration.

Unfortunately, monomeric insulin analog formulations have a propensity to aggregate and to become unstable when exposed to thermo-mechanical stress [Bakaysa, et al., U.S. Patent No. 5,474,978, issued December 12, 1995]. Aggregation may even be manifested as precipitation of higher-order insulin species. In this way, aggregation can prevent reproducible delivery of effective therapeutic doses of monomeric insulin analogs, and may also cause irritation at the administration site or a more systemic immunological response. Insulin analog formulations stabilized against aggregation are desirable.

Formulations of monomeric insulin analogs for use in continuous infusion systems must remain soluble and substantially free of aggregation, even though subjected to the patient's body heat and motion for periods ranging from a few days to several months. Instability is promoted by the higher protein concentrations that are desirable for continuous infusion systems and by the thermo-mechanical stress to which formulations are exposed in continuous infusion systems. Therefore, improvement in the physical and chemical stability of concentrated insulin analog formulations is urgently needed to permit them to be used successfully in continuous infusion systems. Improvement in

the stability of monomeric insulin formulations for uses other than in continuous infusion is also beneficial.

Stabilized formulations of monomeric insulin analogs that are fast-acting, are known. Bakaysa, et al.,
5 U.S. Patent No. 5,474,978 disclose and claim a human insulin analog complex comprising six molecules of a human insulin analog (hexamer complex), two zinc atoms, and at least three molecules of a phenolic preservative, formulations
10 comprising the hexamer complex, and methods of treating diabetes mellitus by administering the formulation. Bakaysa, et al., also claim formulations of the hexamer complex further comprising an isotonicity agent and a physiologically tolerated buffer.

The specification of U.S. Patent No. 5,474,978
15 discloses that the zinc complexes of monomeric insulin analogs may be formulated in the presence of a "physiologically tolerated buffer." Among the buffers mentioned for use in formulations are sodium phosphate, sodium acetate, sodium citrate, and TRIS. The examples in
20 U.S. Patent No. 5,474,978 only describe formulations wherein the buffer is sodium phosphate, and only sodium phosphate buffer is required in a claim (Claim 5). None of the examples in U.S. Patent No. 5,474,978 specifically disclose the use of TRIS buffer in formulations of zinc-monomeric
25 insulin analog complexes.

Monomeric insulin analog formulations containing protamine have also been developed to yield, upon use, an intermediate duration of action. Monomeric insulin analog-protamine formulations are described in U.S. Patent No.
30 5,461,031. Methods for crystallizing monomeric insulin analogs with the basic peptide protamine to yield a neutral protamine suspension are known in the art. In addition, biphasic mixtures containing a monomeric insulin analog solution and a monomeric insulin analog-protamine suspension
35 can be prepared. These mixtures have the optimal time-

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action properties of the analogue in combination with basal activity. Monomeric insulin analog mixtures are also described in U.S. Patent No. 5,461,031.

Monomeric insulin analog-protamine suspension
5 formulations and biphasic mixtures are suitable for use in cartridge container presentations. Yet, because these devices require frequent patient manipulation, increased stress to the preparation results. Protamine salt
10 formulations in particular have limited stability when exposed to thermomechanical stress. Thus, there is a need to develop stable intermediate acting monomeric insulin analog-protamine formulations as well as biphasic mixture formulations.

We have now discovered that when certain
15 physiologically tolerated buffers other than phosphate are employed in formulations of zinc-monomeric insulin analog complexes, protamine salt formulations, or biphasic mixtures of monomeric insulin analog, the physical stability of the formulations is unexpectedly and considerably greater than
20 when phosphate buffer is used. Most advantageous is our discovery that, whereas, soluble formulations of zinc-monomeric insulin analog complexes with a phosphate buffer, such as those specifically exemplified in U.S. Patent No. 5,474,978, are not physically stable enough for long-term
25 administration using continuous infusion pumping systems, the soluble formulations provided by the instant invention are sufficiently stable to be used with safety for long periods of insulin infusion. We have also discovered that the addition of arginine to protamine salt formulations of
30 monomeric insulin analogs results in dramatic improvements in both the chemical and physical stability of the formulation.

Summary of the Invention

Accordingly, the instant invention provides a solution formulation comprising a physiologically-tolerated buffer selected from the group consisting of TRIS and
5 arginine; a monomeric insulin analog; zinc; and a phenolic preservative.

The invention also encompasses an insulin analog formulation comprising a monomeric insulin analog; zinc; a phenolic preservative; protamine; and a buffer selected from
10 the group consisting of TRIS and arginine.

The invention further provides methods of using the insulin analog formulations to treat diabetes and hyperglycemia in a patient in need thereof, which comprises administering to the patient a stable formulation of the
15 present invention.

Detailed Description and Preferred Embodiments

For purposes of the present invention, as disclosed and claimed herein, the following terms and
20 abbreviations have the following meanings.

The term "administer" means to introduce a formulation of the present invention into the body of a patient in need thereof to treat a disease or condition.

The various forms of the verb "to aggregate" refer
25 to a process whereby individual molecules or complexes associate to form aggregates. An aggregate is a polymeric assembly comprising molecules or complexes of monomeric insulin analog. For the purpose of the present invention, the monomeric insulin analog hexamer is not an aggregate,
30 but a complex. Monomeric insulin analogs, and hexamer complexes thereof, have a propensity to aggregate when exposed to thermo-mechanical stress. Aggregation can proceed to the extent that a visible precipitate is formed.

The term "arginine" refers to the amino acid and
35 encompasses the D- and L- enantiomers as well as mixtures

thereof. The term also includes any pharmacologically acceptable salts thereof. Arginine is also known in the art as 1-amino-4-guanidinovaleric acid. Arginine readily forms salts, such as the hydrochloride salt.

5 The term "complex" means a compound in which a transition metal is coordinated to at least one ligand. Ligands include nitrogen-containing molecules, such as proteins, peptides, amino acids, and TRIS, among many other compounds. Monomeric insulin analog can be a ligand of
10 divalent zinc ions.

 The term "continuous infusion system" refers to a device for continuously administering a fluid to a patient parenterally for an extended period of time or for
15 intermittently administering a fluid to a patient parenterally over an extended period of time without having to establish a new site of administration each time the fluid is administered. The fluid contains a therapeutic agent or agents. The device comprises a reservoir for
20 storing the fluid before it is infused, a pump, a catheter, or other tubing for connecting the reservoir to the administration site via the pump, and control elements to regulate the pump. The device may be constructed for
25 implantation, usually subcutaneously. In such a case, the insulin reservoir will usually be adapted for percutaneous refilling. Obviously, when the device is implanted, the contents of the reservoir will be at body temperature, and subject to the patient's body motion.

 An "isotonicity agent" is a compound that is physiologically tolerated and imparts a suitable tonicity to
30 a formulation to prevent the net flow of water across cell membranes that are in contact with the formulation. Compounds, such as glycerin, are commonly used for such purposes at known concentrations. Other possible isotonicity agents include salts, e.g., sodium chloride,
35 dextrose, and lactose.

The terms "monomeric human insulin analog" "monomeric insulin analog" and "human insulin analog" are well-known in the art, and refer generally to fast-acting analogs of human insulin, which include:

- 5 human insulin, wherein Pro at position B28 is substituted with Asp, Lys, Leu, Val, or Ala, and wherein position B29 is Lys or is substituted with Pro; AlaB26-human insulin des(B28-B30) human insulin; and
10 des(B27) human insulin.

Such monomeric insulin analogs are disclosed in Chance, et al., U.S. patent No. 5,514,646, issued May 7, 1996; Chance, et al., U.S. Patent Application Serial No. 08/255,297; Brems, et al., *Protein Engineering*, 6:527-533 (1992);
15 Brange, et al., EPO publication No. 214,826 (published March 18, 1987); and Brange, et al., *Current Opinion in Structural Biology* 1:934-940 (1991). The monomeric insulin analogs employed in the present formulations are properly cross-linked. A properly cross-linked insulin analog contains
20 three disulfide bridges: one between position 7 of the A-chain and position 7 of the B-chain, a second between position 20 of the A-chain and position 19 of the B-chain, and a third between positions 6 and 11 of the A-chain.

The term "phenolic preservative" as used herein
25 refers to chlorocresol, m-cresol, phenol, or mixtures thereof.

As used herein, the noun "stability" refers to the physical stability of formulations of monomeric insulin analogs. Physical instability of a protein formulation may
30 be caused by aggregation of the protein molecules to form higher order polymers or even precipitates. A "stable" formulation is one wherein the degree of aggregation of proteins therein is acceptably controlled, and does not increase unacceptably with time. Monomeric insulin analog
35 formulations have a propensity to aggregate when exposed to

thermo-mechanical stress. Physical stability may be assessed by methods well-known in the art, including measurement of a sample's apparent attenuation of light (absorbance, or optical density). Such a measurement of
5 light attenuation relates to the turbidity of a formulation. Turbidity is produced by aggregation or precipitation of proteins or complexes in the formulation. Other methods for assessing physical stability are well-known in the art.

The term "treating" refers to the management and
10 care of a patient having diabetes or hyperglycemia, or other condition for which insulin administration is indicated for the purpose of combating or alleviating symptoms and complications of those conditions. Treating includes administering a formulation of present invention to prevent
15 the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder.

The term "TRIS" refers to 2-amino-2-hydroxymethyl-1,3,-propanediol, and to any pharmacologically acceptable
20 salt thereof. The free base and the hydrochloride form are two common forms of TRIS. TRIS is also known in the art as trimethylol aminomethane, tromethamine, and tris(hydroxymethyl)aminomethane.

That the instant invention provides formulations
25 of monomeric insulin analogs having greatly increased physical stability relative to those known in the art will be readily appreciated from the following data.

Formulations comprising a monomeric insulin analog, Lys^{B28}Pro^{B29}-Human Insulin Analog, and TRIS,
30 prepared essentially as described in Example 3 herein, were subjected to accelerated stability testing as described below. Samples of the prepared formulations were placed into pre-cleaned, 2 mL capacity, glass HPLC autosampler vials. Each vial contained three Teflon[®] balls
35 approximately 3/16 inch in diameter. Air was completely

displaced from the vial by the sample of formulation. After sealing, the vials were continuously shaken at 40 Hz (20 x g, average linear acceleration) at a peak-to-peak amplitude of 12 mm, and at 37°C to provide a relatively high level of mechanical energy input to the formulations at a temperature that favors aggregation and physical instability. The vials were positioned on the shaker such that their long dimension (i.e., top to bottom) was oriented parallel to the direction of linear acceleration - that is, they lay on their sides on the surface of the shaker. It has been shown for insulin formulations that increased stability under the accelerated conditions described above correlates with greatly increased in-use stability.

The optical density at 450 nm of sample formulations and of control formulations was measured periodically using a Shimadzu 1201 spectrophotometer. Control formulations were prepared in the same manner as sample formulations, but were stored at 4°C without agitation. The net optical density was calculated for a sample by subtracting the optical density of the control from the optical density of the sample. Values in Table 1 are the average net optical density and standard deviation for the number of samples (n) given. Sample and control formulations containing phosphate as the buffer (pH 7.4 ± 0.1) were prepared essentially as described in Example 4.

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Table 1. Effects of Buffer and Time of Exposure to High Mechanical Energy Input at 37°C on the Turbidity (Optical Density at 450 nm) of Formulations of Lys^{B28}Pro^{B29}-Human Insulin Analog

	Optical Density at 450 nm			
	16 hours	70 hours	100 hours	500 hours
Example 3 (TRIS)	0.02 ± 0.01 n=5	0.03 ± 0.02 n=5	0.01 ± 0.01 n=5	0.04 ± 0.01 n=4
Example 4 (Phosphate)	0.81 ± 0.71 n=5	N.D.	N.D.	N.D.

N.D. = not determined

Under the conditions described above, turbidity in the formulations having a phosphate buffer reached very high, and unacceptable levels by 16 hours (Table 1, Example 4) compared with control formulations containing phosphate that were stored at 4°C without agitation. On the other hand, the optical density of formulations having TRIS as the buffer remained virtually the same as the optical density in the control for 500 hours for formulations containing TRIS (Example 3). The data in Table 1 clearly demonstrate that replacement of phosphate buffer with TRIS buffer in formulations of Lys^{B28}Pro^{B29}-Human Insulin Analog drastically increases the stability of the formulations. Based on observations with other insulin formulations, it is believed that the surprising and significant stability of formulations of monomeric insulin analog in TRIS buffer in the accelerated test will translate into "in-use" stability far greater than 500 hours because the energy input is greater in the accelerated test than during expected uses.

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Formulations comprising a monomeric insulin analog, Lys^{B28}Pro^{B29}-Human Insulin Analog, and either TRIS, phosphate, or L-arginine as buffers were prepared essentially as described in Examples 3, 4, and 5, respectively. Three lots of Lys^{B28}Pro^{B29}-Human Insulin Analog were used to prepare the formulations. For each combination of analog lot and buffer, six samples were subjected to stability testing as described above. Four different shakers were used to impart mechanical energy to the vials. Each shaker had at least one sample of each lot and buffer combination. Stability of the formulations was assessed periodically by measuring the optical density of samples and controls as described above. Results are in Table 2. Values in Table 2 are the average net optical density and standard deviation of six samples for each lot and buffer.

Table 2. Effects of Buffer, Lot of Analog, and Time of Exposure to High Mechanical Energy Input at 37°C on the Turbidity (Optical Density at 450 nm) of Formulations of LysB28proB29-Human Insulin Analog

Buffer	Analog Lot	Optical Density at 450 nm			
		23 hours	47 hours	87 hours	139 hours
TRIS	Lot 1	0.02 ±	0.06 ±	0.05 ±	0.00 ±
		0.02	0.02	0.02	0.02
	Lot 2	0.00 ±	0.04 ±	0.03 ±	0.00 ±
		0.01	0.02	0.01	0.02
	Lot 3	0.02 ±	0.05 ±	0.04 ±	0.01 ±
		0.02	0.03	0.03	0.02
Arginine	Lot 1	0.01 ±	0.04 ±	0.04 ±	2.12 ±
		0.02	0.02	0.02	1.03
	Lot 2	0.01 ±	0.04 ±	0.06 ±	1.80 ±
		0.02	0.02	0.08	0.60
	Lot 3	0.00 ±	0.03 ±	1.84 ±	N.D.
		0.02	0.02	0.66	
Phosphate	Lot 1	0.13 ±	2.68 ±	2.61 ±	N.D.
		0.06	0.17	0.11	
	Lot 2	0.21 ±	2.14 ±	2.75 ±	N.D.
		0.24	0.75	0.14	
	Lot 3	0.29 ±	2.75 ±	2.79 ±	N.D.
		0.23	0.14	0.11	

Under the conditions described above, turbidity in the formulations having a phosphate buffer reached very high, and unacceptable levels by 23 hours, regardless of the lot of insulin analog used (Table 2). By contrast, turbidity in formulations having TRIS as the buffer remained essentially unchanged for 139 hours, regardless of the lot of insulin used. Formulations containing L-arginine buffer demonstrated better physical stability compared with

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formulations containing phosphate, and the duration of their stability depended somewhat on the lot of insulin analog used. The data in Table 2 clearly demonstrate that formulations of Lys^{B28}Pro^{B29}-Human Insulin Analog comprising

5 TRIS buffer or L-arginine buffer at pH 7.4 remain stable against aggregation for markedly longer periods of time than do formulations comprising a phosphate buffer. Again, it is believed that the surprising and significant stability of formulations of monomeric insulin analog in TRIS and in L-

10 arginine buffer will translate into "in-use" stability far greater than observed in the accelerated test because the energy input is greater in the accelerated test than during expected uses.

Susceptibility to changes in morphology and

15 appearance for Lys^{B28}Pro^{B29} suspension formulations were evaluated by the Physical Stability Stress Test (PSST). In this thermomechanical method, preparations were sealed with no headspace in a fixed volume container with a glass bead. The containers were placed in a chamber at elevated

20 temperature (approximately 37 degrees C), rotated at a fixed speed (about 30 rpm) for a defined time (about 4 hours) and then held quiescent for the remainder of a 24 hour period. Containers were evaluated for changes and removed from testing when it was determined that aggregation (clumping)

25 had occurred. Longer periods on test without a failure, as well as larger numbers of containers remaining on test, were equated with increased physical stability.

Two different mixtures containing Lys^{B28}Pro^{B29} and Lys^{B28}Pro^{B29}-protamine crystals were tested. The ratio of

30 Lys^{B28}Pro^{B29} to Lys^{B28}Pro^{B29}-protamine for the low mixture was 25:75 and for the high mixture was 75:25. The mixtures were prepared as described in Examples 6 and 7. When the low mixture was tested using the PSST method, only formulations containing arginine had containers remaining

after 18 days. Two of the test samples had containers remaining out to 44 days. The PSST on high mixtures showed similar results with the formulations containing arginine having approximately 50% of the containers remaining after 5 36 days of testing whereas the control formulations containing phosphate buffer had 0 to 5 % of the containers remaining after 36 days.

Preferred monomeric insulin analogs for use in the formulations of the present invention are Lys^{B28}Pro^{B29}-human 10 insulin, Asp^{B28}-human insulin, and Ala^{B26}-human insulin.

The concentration of monomeric insulin analog in the present formulations ranges from 1.2 mg/mL to 50 mg/mL. A preferred range of analog concentration is from about 3.0 mg/mL to about 35 mg/mL. More preferred concentrations are 15 about 3.5 mg/mL, about 7 mg/mL, about 14 mg/mL, about 17.5 mg/mL, and about 35 mg/mL which correspond approximately to formulations having about 100 units, about 200 units, about 400 units, about 500 units, and about 1000 units of insulin activity per mL, respectively.

20 The concentration of zinc in the formulations ranges from about 4.5 mg/mL to about 370 mg/mL, and must be such that at least two zinc atoms are available to complex with the six insulin molecules in each hexamer. The ratio of total zinc (complexed zinc plus uncomplexed zinc) to 25 insulin analog hexamer should be between 2 and 4. A ratio of about 3 to about 4 atoms of total zinc per insulin analog hexamer complex is preferred.

The minimum concentration of phenolic preservative that is required to form the monomeric insulin analog 30 hexamer in the present formulations. For some purposes, such as to meet compendial preservative effectiveness requirements for multi-use formulations, the concentration of phenolic preservative in the present formulations may be increased above that required to form hexamers to an amount 35 necessary to maintain preservative effectiveness. The

concentration of preservative necessary for effective preservation depends on the preservative used, the pH of the formulation, and whether substances that bind or sequester the preservative are also present. Generally, the amount
5 necessary can be found in, e.g., WALLHAUSER, K.DH., DEVELOP. BIOL. STANDARD. 24, pp. 9-28 (Basel, S. Krager, 1974). When formulated, the insulin analog hexamer complex used in the present formulation binds as many as seven phenolics, though generally, only six phenolics are bound to the hexamer. A
10 minimum of about three phenolics is required for hexamer formation. When preservative is required for antimicrobial effectiveness, the preferred phenolic concentration is about 23 mM to about 35 mM. M-cresol and phenol, either separately or in mixtures, are preferred preservatives.

15 The formulations may optionally contain an isotonicity agent. The formulations preferably contain an isotonicity agent, and glycerin is the most preferred isotonicity agent. The concentration of glycerin, when it is used, is in the range known in the art for insulin
20 formulations, preferably about 16 mg/mL.

The pH of the formulations is controlled by a buffering agent, such as TRIS or L-arginine. The concentration of the buffers is not thought to play a critical role in obtaining the object of the invention, and
25 should be such as to provide adequate buffering of the pH during storage to maintain the pH at a target pH ± 0.1 pH unit. The preferred pH is between about 7 and about 8, when measured at a temperature of about 22°C.

Other additives, such as a pharmaceutically
30 acceptable solubilizers like Tween 20[®] (polyoxyethylene (20) sorbitan monolaurate), Tween 40[®] (polyoxyethylene (20) sorbitan monopalmitate), Tween 80[®] (polyoxyethylene (20) sorbitan monooleate), Pluronic F68[®] (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene
35 glycol) may optionally be added to the formulation. These

additives are not required to achieve the great advantage of the present invention, but may be useful if the formulations will contact plastic materials.

The present invention also encompasses protamine
5 salt preparations with varying proportions of soluble
fractions of monomeric insulin analogs. No specific
conformational requirements of the insulin molecule are
required to stabilize the formulation with arginine,
although excipients like zinc and preservatives normally
10 added to insulin formulations (discussed above) may work in
concert with arginine to enhance stabilization. Arginine
concentrations range from 1 to 100 mM in formulations
containing protamine. Most preferred is an arginine
concentration range of 5 to 25 mM. Arginine can be added as
15 a supplement to solutions or precipitated suspensions
already containing zinc ions and phenolic preservatives.

Administration may be via any route known to be
effective by the physician of ordinary skill. Parenteral
administration is preferred. Parenteral administration is
20 commonly understood as administration by other than a
gastro-intestinal route. Preferred parenteral routes for
administering the formulations of the present invention
include intravenous, intramuscular, subcutaneous,
intraperitoneal, intraarterial, nasal, pulmonary, and buccal
25 routes. Intravenous, intraperitoneal, intramuscular, and
subcutaneous routes of administration of the compounds used
in the present invention are more preferred parenteral
routes of administration. Intravenous, intraperitoneal, and
subcutaneous routes of administration of the formulations of
30 the present invention yet more highly preferred.

Administration via certain parenteral routes may
involve introducing the formulations of the present
invention into the body of a patient through a needle or a
catheter, propelled by a sterile syringe or some other
35 mechanical device such as an continuous infusion system. A

formulation provided by the present invention may be administered using a syringe, injector, pump, or any other device recognized in the art for parenteral administration.

5 A formulation of the present invention may also be administered as an aerosol for absorption in the lung or nasal cavity. The formulations may also be administered for absorption through the mucus membranes, such as in buccal administration.

10 The amount of a formulation of the present invention that is administered to treat diabetes or hyperglycemia depends on a number of factors, among which are included, without limitation, the patient's sex, weight and age, the underlying causes of the condition or disease to be treated, the route of administration and
15 bioavailability, the persistence of the administered monomeric insulin analog in the body, the formulation, and the potency of the monomeric insulin analog. Where administration is intermittent, the amount per
20 administration should also take into account the interval between doses, and the bioavailability of the monomeric insulin analog from the formulation. Administration of the formulation of the present invention could be continuous. It is within the skill of the ordinary physician to titrate the dose and infusion rate or frequency of administration of
25 the formulation of the present invention to achieve the desired clinical result.

Monomeric insulin analogs used in the present invention can be prepared by any of a variety of recognized peptide synthesis techniques including classical solution
30 methods, solid phase methods, semi-synthetic methods, and recombinant DNA methods. Chance, et al., U.S. Patent No. 5,514,646, issued May 7, 1996, discloses the preparation of various monomeric insulin analogs with sufficient detail to enable one skilled in the art to prepare any of the
35 monomeric insulin analogs used in the present invention.

Both zinc and a phenolic preservative are essential to achieve a complex that is stable and capable of rapid dissociation and onset of action. The hexamer complex consists of two zinc ions per hexamer of human insulin analog, and at least three molecules of a phenolic preservative selected from the group consisting of chlorocresol, m-cresol, phenol, and mixtures thereof.

Soluble monomeric insulin analog is converted to the hexamer complex by dissolving the monomeric insulin analog in a diluent containing the phenolic preservative in suitable quantities at a pH of about 7 to about 8 and then adding zinc. Zinc is preferably added as a zinc salt, such as, without limitation, zinc acetate, zinc bromide, zinc chloride, zinc fluoride, zinc iodide, and zinc sulfate. The skilled artisan will recognize that there are many other zinc salts which also might be used to make the monomeric insulin analog complexes that are part of the present invention. Preferably, zinc acetate, zinc oxide, or zinc chloride is used because these compounds do not add new chemical ions to commercially accepted processes.

Dissolution of the monomeric insulin analog may be aided by what is commonly known as "acid dissolution." For acid dissolution, the pH the aqueous solvent is lowered to about 3.0 to 3.5 with a physiologically tolerated acid, preferably HCl, to aid in the dissolution of the monomeric analog. Other physiologically tolerated acids include, without limitation, acetic acid, citric acid, and sulfuric acid. Phosphoric acid is preferably not used to adjust pH in preparing the formulations of the present invention. The pH is then adjusted with a physiologically tolerated base, preferably sodium hydroxide, to about pH 7.3 to 7.5. Other physiologically tolerated bases include, without limitation, potassium hydroxide and ammonium hydroxide. Thereafter, the phenolic preservative and zinc are added.

Parenteral formulations of the present invention can be prepared using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of monomeric insulin analog in water is combined with the desired preservative, a zinc compound, and the buffering agent, in water in sufficient quantities to prepare the hexamer complex. The formulation is generally sterile filtered prior to administration. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, the order in which pH is adjusted, if any, the temperature and ionic strength at which the formulation is prepared, may be optimized for the concentration and means of administration used.

The following examples and preparations are provided merely to further illustrate the preparation of the formulations of the invention. The scope of the invention is not limited to the following examples.

Example 1

Preparation of a U100 Soluble Formulation Containing Lys^{B28}Pro^{B29}-Human Insulin Analog and TRIS

An amount of Lys^{B28}Pro^{B29}-Human Insulin Analog-Zinc Crystals calculated to yield 100 Units of insulin activity per milliliter in the final formulation were suspended in an aqueous solution containing 0.715 mg/mL phenol, 1.76 mg/mL m-cresol, 16 mg/mL glycerin, and zinc oxide. The insulin analog-zinc crystals contained about 0.36% zinc on a weight basis. The concentration of zinc oxide in the aqueous diluent was such as to supplement the final zinc ion concentration of the formulation to about 0.025 mg per 100 units of insulin activity. A volume of 10% hydrochloric acid was added to adjust the pH to 2.8 to 3.0. After stirring to dissolve the crystals, aliquots of 10% sodium hydroxide solution were carefully added to adjust the pH to 7.4 to 7.7. A volume of a stock solution of TRIS (50

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mg/mL, pH 7.4, measured at ambient temperature, i.e., about 22°C) calculated to give a concentration of TRIS of 2 mg/mL in the final formulation, was added to the insulin analog solution. Water was added to dilute the formulation to the
5 final volume. The formulation was sterile-filtered using a 0.2 micron filter.

Example 2

10 Preparation of a U100 Soluble Formulation Containing
Lys^{B28}Pro^{B29}-Human Insulin Analog and L-Arginine
The process described in Example 1 was followed until addition of the buffer. Then, instead of adding a volume of a TRIS stock solution, a volume of a stock solution of L-arginine (200 mM, pH 7.4), calculated to give
15 a concentration of L-arginine of 20 mM in the final formulation, was added to the insulin analog solution. Water was added to dilute the formulation to the final volume. The formulation was sterile-filtered using a 0.2 micron filter.

Example 3

Preparation of a U400 Soluble Formulation Containing
Lys^{B28}Pro^{B29}-Human Insulin Analog and TRIS
An amount of Lys^{B28}Pro^{B29}-Human Insulin Analog-
25 Zinc Crystals calculated to yield 400 Units of insulin activity per milliliter in the final formulation were suspended in an aqueous solution containing 0.715 mg/mL phenol, 1.76 mg/mL m-cresol, 16 mg/mL glycerin, and zinc oxide. The insulin analog-zinc crystals contained about
30 0.36% zinc on a weight basis. The concentration of zinc oxide in the aqueous diluent was such as to supplement the final zinc ion concentration of the formulation to about 0.025 mg per 100 units of insulin activity. A volume of 10% hydrochloric acid was added to adjust the pH to 2.8 to 3.0.
35 After stirring to dissolve the crystals, aliquots of 10% sodium hydroxide solution were carefully added to adjust the

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pH to 7.4 to 7.7. A volume of a stock solution of TRIS (50 mg/mL, pH 7.4, measured at ambient temperature, i.e., about 22°C) calculated to give a concentration of TRIS of 2 mg/mL in the final formulation was added to the insulin analog solution. Water was added to dilute the formulation to the final volume. The formulation was sterile-filtered using a 0.2 micron filter.

Example 4

Preparation of a U400 Soluble Formulation Containing Lys^{B28}Pro^{B29}-Human Insulin Analog and Phosphate

An amount of Lys^{B28}Pro^{B29}-Human Insulin Analog-Zinc Crystals calculated to yield 400 Units of insulin activity per milliliter in the final formulation were suspended in an aqueous solution containing 0.715 mg/mL phenol, 1.76 mg/mL m-cresol, 16 mg/mL glycerin, and zinc oxide. The insulin analog-zinc crystals contained about 0.36% zinc on a weight basis. The concentration of zinc oxide in the aqueous diluent was such as to supplement the final zinc ion concentration of the formulation to about 0.025 mg per 100 units of insulin activity. A volume of 10% hydrochloric acid was added to adjust the pH to 2.8 to 3.0. After stirring to dissolve the crystals, aliquots of 10% sodium hydroxide solution were carefully added to adjust the pH to 7.4 to 7.7. A volume of a stock solution of dibasic sodium phosphate calculated to give a concentration of dibasic sodium phosphate of 3.78 mg/mL, pH 7.4 ± 0.1 in the final formulation was added to the insulin analog solution. Water was added to dilute the formulation to the final volume. The formulation was sterile-filtered using a 0.2 micron filter.

Example 5Preparation of a U400 Soluble Formulation Containing
Lys^{B28}Pro^{B29}-Human Insulin Analog and L-Arginine

The process described in Example 3 was followed

5 until addition of the buffer. Then, instead of adding a
volume of a TRIS stock solution, a volume of a stock
solution of L-arginine (200 mM, pH 7.4) calculated to give a
concentration of L-arginine of 20 mM in the final
formulation was added to the insulin analog solution. Water
10 was added to dilute the formulation to the final volume.
The formulation was sterile-filtered using a 0.2 micron
filter.

Example 6

15 Preparation of U100 Lys^{B28}Pro^{B29}-Human Insulin Analog High
Mixture Formulation (75% v/v soluble, 25% v/v neutral
protamine Lys^{B28}Pro^{B29}) Containing L-Arginine

A. Preparation of Neutral Protamine Lys^{B28}Pro^{B29}

An amount calculated to contain 200 U/mL of
20 Lys^{B28}Pro^{B29} Zinc Insulin Crystals was suspended in an
aqueous solution containing 0.715 mg/mL phenol, 1.76 mg/mL
m-cresol, 16 mg/mL glycerin, and zinc oxide acidified with
hydrochloric acid so as to supplement the final zinc ion
concentration to 0.025 mg/100 U. A volume of 10%
25 hydrochloric acid was added to adjust the solution to pH 2.8
to 3.0. After stirring to dissolve, 10% sodium hydroxide
solution was added to adjust the solution to pH 7.4 to 7.7.
A volume equivalent to a final 3.78 mg/mL formulation
concentration of 75.6 mg/mL dibasic sodium phosphate
30 solution at pH 7.2 was added. Following dissolution of the
precipitated solids and titration to maintain pH 7.4, water
was added to dilute the formulation to final volume, after
which the solution was filtered.

Solid protamine sulfate, calculated to contain 0.6
35 mg/100 U protamine base, was dissolved in an aqueous

solution containing 0.715 mg/mL phenol, 1.76 mg/mL m-cresol and 16 mg/mL glycerin. Solid dibasic sodium phosphate was added so that the formulation concentration was 3.78 mg/mL. The solution was adjusted to pH 7.4 with 10% hydrochloric acid, diluted to final volume with water, and filtered.

Both the 200 unit Lys^{B28}Pro^{B29} solution and the protamine solution were equilibrated at 15°C. The protamine solution was added to the Lys^{B28}Pro^{B29} solution and the resulting suspension allowed to incubate undisturbed at 15°C for 24 hours.

B. Preparation of Lys^{B28}Pro^{B29} High Mixture

An amount of Lys^{B28}Pro^{B29} 100 unit solution containing L-arginine prepared in Example 2 corresponding to 75% of the final volume was added to a calculated volume of 100 U/mL neutral protamine Lys^{B28}Pro^{B29}. The suspension was stirred at ambient temperature.

Example 7

Preparation of U100 Lys^{B28}Pro^{B29}-Human Insulin Analog Low Mixture Formulation (25% v/v soluble, 75% v/v neutral protamine Lys^{B28}Pro^{B29}) Containing L-Arginine

A. Preparation of Neutral Protamine Lys^{B28}Pro^{B29}

An amount calculated to contain 200 U/mL of Lys^{B28}Pro^{B29} Zinc Insulin Crystals was suspended in an aqueous solution containing 0.715 mg/mL phenol, 1.76 mg/mL m-cresol, 16 mg/mL glycerin, and zinc oxide acidified with hydrochloric acid so as to supplement the final zinc ion concentration to 0.025 mg/100 U. A volume of 10% hydrochloric acid was added to adjust the solution to pH 2.8 to 3.0. After stirring to dissolve, 10% sodium hydroxide solution was added to adjust the solution to pH 7.4 to 7.7. A volume equivalent to a final 3.78 mg/mL formulation concentration of 75.6 mg/mL dibasic sodium phosphate

solution at pH 7.2 was added. Following dissolution of the precipitated solids and titration to maintain pH 7.4, water was added to dilute the formulation to final volume, after which the solution was filtered.

- 5 Solid protamine sulfate, calculated to contain 0.6 mg/100 U protamine base, was dissolved in an aqueous solution containing 0.715 mg/mL phenol, 1.76 mg/mL m-cresol and 16 mg/mL glycerin. Solid dibasic sodium phosphate was added so that the formulation concentration was 3.78 mg/mL.
- 10 The solution was adjusted to pH 7.4 with 10% hydrochloric acid, diluted to final volume with water, and filtered.

- Both the U200 Lys^{B28}Pro^{B29} solution and the protamine solution were equilibrated at 15 C. The protamine solution was added to the Lys^{B28}Pro^{B29} solution and the
- 15 resulting suspension allowed to incubate undisturbed at 15 C for 24 hours.

B. Preparation of Lys^{B28}Pro^{B29} Low Mixture

- An amount of Lys^{B28}Pro^{B29} U100 solution containing
- 20 L-arginine prepared in Example 2 corresponding to 25% of the final volume was added to a calculated volume of 100 U/mL neutral protamine Lys^{B28}Pro^{B29}. The suspension was stirred at ambient temperature.

We claim:

1. A solution formulation comprising:
a physiologically tolerated buffer selected from the group
5 consisting of TRIS and arginine; a monomeric insulin
analog; zinc; and a phenolic preservative.

2. The formulation of Claim 1, wherein the
monomeric insulin analog is Lys^{B28}Pro^{B29}-human insulin and
10 the buffer is TRIS.

3. The formulation of Claim 1, wherein the
monomeric insulin analog is Asp^{B28}-human insulin and the
buffer is TRIS.

4. The formulation of Claim 2 further comprising
an isotonicity agent and wherein the pH of the formulation
is between pH 7.0 and pH 8.0 when measured at a temperature
of 22°C.

5. The formulation of Claim 4, wherein the
concentration of Lys^{B28}Pro^{B29}-human insulin is between about
100 and about 400 units per milliliter.

6. The formulation of Claim 5, wherein TRIS is
present at a concentration of about 2 mg/mL; glycerol is
the isotonicity agent and is present at a concentration of
about 16 mg/mL; and m-cresol is present at a concentration
of about 1.76 mg/mL and phenol is present at a concentration
30 of about 0.715 mg/mL.

7. A stable, soluble formulation of a monomeric insulin analog for use in a continuous infusion system, consisting essentially of: an isotonicity agent; a buffer selected from the group consisting of TRIS and arginine; a monomeric insulin analog; zinc; and a phenolic preservative.

8. The insulin analog formulation of Claim 1, which further comprises protamine.

9. The formulation of Claim 8, wherein the insulin analog is Lys^{B28}Pro^{B29}.

10. The formulation of Claim 8, wherein the insulin analog is Asp^{B28}.

11. A method for treating diabetes comprising administering an effective dose of the formulation of Claim 1 to a patient in need thereof.

12. The method of Claim 11, wherein the formulation is administered using a continuous infusion system.

13. A method for treating hyperglycemia comprising administering an effective dose of the formulation of Claim 1 to a patient in need thereof.

14. The method of Claim 13, wherein the formulation is administered using a continuous infusion system.

5 15. A method for treating diabetes comprising administering an effective dose of the formulation of Claim 8 to a patient in need thereof.

10 16. A method for treating hyperglycemia comprising administering an effective dose of the formulation of Claim 8 to a patient in need thereof.

ABSTRACT

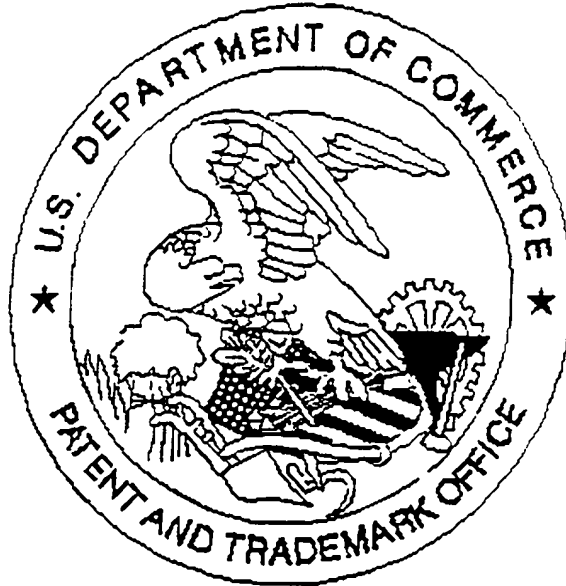
The present invention provides a monomeric insulin analog formulation stabilized against aggregation in which
5 the buffering agent is either TRIS or arginine. The stable formulations of the present invention are useful for treating diabetes, and are particularly advantageous in treatment regimes requiring lengthy chemical and physical stability, such as, in continuous infusion systems.

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